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TO: All Field Personnel with Responsibility for VIOXX  
 FROM: Market Integration Team for VIOXX  
 SUBJECT: Top Ten Obstacle Handlers

Enclosed is the complete Obstacle Handling Guide for VIOXX. This Guide includes all obstacle responses issued since the launch of VIOXX. Though it is important for you to be familiar with all of the obstacle handlers, the following Top Ten Obstacle Handlers are the most important obstacle handlers at this time as they center around current issues in the field.

### Cardiovascular Events

Obstacle Response #7- "Can VIOXX be used in patients using low dose aspirin?"

Obstacle Response #23- "I am concerned about the cardiovascular effects of VIOXX."

Obstacle Response #38- "The competition has been in my office telling me that the incidence of heart attacks (or cardiovascular events) is greater with VIOXX than Celebrex." OR "I just read (or heard) a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

### Renal Effects

Obstacle Response #4- "I am concerned about the potential edema that occurs with VIOXX."

Obstacle Response #20- "Can I use VIOXX with Ace Inhibitors?"

Obstacle Response #31- "I am concerned about dose-related increases in hypertension with VIOXX."

### VIOXX 50mg Tablet

Obstacle Responses #9 and 9a- "Why wasn't VIOXX 50mg studied for longer than five days in acute pain?" OR "VIOXX cannot be used for longer than five days when treating patients for acute pain."

Obstacle Response #30- "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

### General

Obstacle Response #26- "I use Celebrex. I'm concerned about the safety profile of VIOXX."

Obstacle Response #34- "I understand the new COX-2 agent, MOBIC, was just approved."

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OBSTACLE  
RESPONSE GUIDE  
VIOXX

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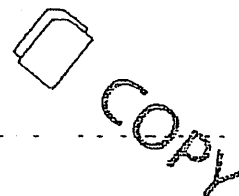


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## Obstacle Response Guide

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### List of Obstacles

1. "There is no difference between VIOXX and Celebrex. Why should I use VIOXX?"
  2. "I can't use VIOXX with patients being treated with methotrexate."
  3. "Is VIOXX contraindicated in patients being treated with warfarin?"
  - 3a. I received this letter from Searle about Celebrex and warfarin. What can you tell me about it and VIOXX?
  4. "I'm concerned about the potential edema that occurs with VIOXX."
  5. "It is my understanding that VIOXX was denied an indication for RA by the FDA."
- 
6. "VIOXX is not an anti-inflammatory drug."
  7. "Can VIOXX be used in patients using low dose aspirin?"
  8. "I understand that VIOXX has sulfur as part of its chemical structure. Is it contraindicated for patients with "sulfa allergies?"
  9. "Why wasn't VIOXX 50 mg studied for longer than five days in acute pain?"
  - 9a. "VIOXX cannot be used for longer than five days when treating patients for acute pain"
  10. "Why didn't you compare VIOXX to higher doses of ibuprofen or naproxen sodium for the management of pain?"
  11. "When do I prescribe VIOXX 12.5 mg, 25 mg, or 50 mg once daily?"

12. "Can I use VIOXX in patients with renal impairment?"

13. "Why doesn't VIOXX have a 50 mg tablet?" DELETED

14. "How does your price compare to Celebrex and other branded NSAIDs?"

15. "Isn't a 17-hour half-life inconsistent with once daily dosing?"

16. "Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should I be concerned about the fact that COZAAR is metabolized by the P450 system?"

or

"How is the CYP450 issue with Celebrex any different from COZAAR?"

17. "Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should I be concerned about the fact that ZOCOR is metabolized by the P450 system?"

or

"How is the CYP450 issue with Celebrex any different from ZOCOR?"

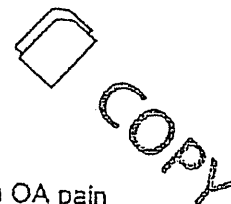
18. "The pain studies for VIOXX were not well designed."

19. "What hepatic effects can I expect with VIOXX?"

20. "Can I use VIOXX with ACE inhibitors?"

21. "VIOXX is only comparable to a single dose of naproxen."

22. "I've been told that 45% of VIOXX is metabolized through the cytochrome P450 system."

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23. "I am concerned about the cardiovascular effects of VIOXX."
  24. "Your PI states that VIOXX provided a significant reduction in OA pain after one to two weeks. Why should I use VIOXX when Celebrex states OA patients achieved significant reduction in pain within 24-48 hours after initiation of dosing?"
  25. "Do I have to discontinue VIOXX pre or post-operatively?"
  26. "I use Celebrex. I'm concerned about the safety profile of VIOXX. (Cumulative vs. Additive clarification)"
  27. "Why are you telling me not to prescribe Celebrex for sulfa-allergic patients when Hyzaar has the same contraindication?"
  28. "The two recent JAMA articles showed that Celebrex provided greater reductions in events than VIOXX." OR "It looks like there are still a lot of PUB's in the VIOXX group; why is the reduction only 50% and not 100%?"
  29. "I understand Celebrex just received an FDA approval for prevention of cancer. Is VIOXX receiving a similar indication soon?"
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30. "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."
  31. "I am concerned with dose-related increases in hypertension with VIOXX."
  32. "Celebrex must be a safer agent. Unlike VIOXX, Celebrex outcomes data did not show any increases in myocardial infarctions or stroke."
  33. "Why didn't VIOXX report the p-values for its' OUTCOMES STUDY?"  
DELETED
  34. "I understand the new COX-2 agent, Mobic, was just approved."

35. "The Mobic representative told me that Mobic is 20% less expensive than VIOXX. I am considering using Mobic due to the cost advantage."

36. "I am impressed with Mobic's tremendous amount of worldwide experience."

37. "The Mobic representative has shown me data from two large-scale studies, the MELISSA and SELECT trials, which emphasized Mobic's GI tolerability. I find these studies very comprehensive and impressive."

38. "The competition has been in my office telling me that the incidence of heart attacks [or cardiovascular events] is greater with VIOXX than Celebrex."

OR

"I just read [or heard] a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

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Clarify: Doctor, while they both work by inhibiting COX-2, I would like to point out some key clinical areas of distinction that may be important to you and your patients.

#### INDICATIONS

Once daily VIOXX is indicated for the relief of the signs and symptoms of OA, management of acute pain in adults and treatment of primary dysmenorrhea, representing all of the indications that were submitted to the FDA for approval of VIOXX.

Celecoxib is indicated for the signs and symptoms of OA and RA.

#### Reference:

A&A Training Program ⇒ Module 5 (NSAIDs)  
VIOXX PI ⇒ Indications and Usage (V22)  
Celecoxib PI ⇒ Indications and Usage (C23)

#### CONTRAINDICATIONS

Both VIOXX and celecoxib are contraindicated in patients who are allergic to them, aspirin or other NSAIDs. Once daily VIOXX is not contraindicated in patients with sulfonamide allergies, commonly known as sulfa allergies.

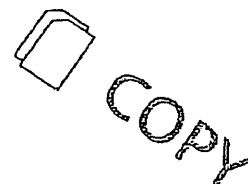
In contrast, celecoxib is contraindicated in patients with allergic-type reactions to sulfonamides. This contraindication is unique to celecoxib, due to its molecular structure, and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX offers simplicity - simplified prescribing without having to worry about a sulfonamide allergy contraindication.

Reference:

VIOXX PI  $\Rightarrow$  Contraindication (V23)

Celecoxib PI  $\Rightarrow$  Contraindication (C24)

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**DOSING**

Doctor, VIOXX offers dosing simplicity of one tablet, once daily dosing for all indications – the relief of the signs and symptoms of OA, management of acute pain in adults, and the treatment of primary dysmenorrhea. With celecoxib, each time you see an OA patient you must decide whether to prescribe it once a day or twice a day. VIOXX also offers the option to increase the dose to 25 mg once daily for OA patients who need additional relief. Celecoxib has one dose – 200 mg, and its label states that no additional efficacy is seen with 200 mg BID.

Reference:

VIOXX PI  $\Rightarrow$  Dosage and Administration  $\Rightarrow$  Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)

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Celecoxib PI  $\Rightarrow$  Dosage and Administration  $\Rightarrow$  Osteoarthritis (C54)

**METABOLISM**

Once daily VIOXX is metabolized primarily through cytosolic enzymes in the liver. Unlike once daily VIOXX, celecoxib is metabolized through the cytochrome P450 system.

(Remember to provide appropriate balancing information on use in hepatic insufficiency and hepatic effects.)

Reference:

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Pharmacokinetics  $\Rightarrow$  Metabolism (V7)



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#### COMPREHENSIVE CLINICAL STUDIES

Once daily VIOXX has been comprehensively studied. In OA patients, once daily VIOXX was compared to diclofenac in two 1-year studies. The endoscopy studies were six-month studies. We have data on serious upper GI events out to one year. This was the most comprehensive clinical program ever run by Merck. Let me share some of the data with you...

VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen and was consistent across all studies.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

#### **Reference:**

VIOXX PI  $\Rightarrow$  Clinical Studies  $\Rightarrow$  OA (V16)

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~~2. I cannot use VIOXX with patients being treated with methotrexate.~~

Doctor, once daily VIOXX is not contraindicated in patients receiving methotrexate. No dosage adjustments of once daily VIOXX and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX.

If probed further:

Doctor, according to the product circular for once daily VIOXX, at doses of 75 mg (which is 3 to 6 times the OA therapeutic dose), once daily VIOXX increased plasma concentrations of methotrexate by 23%. At 24 hours post dose or at the trough period, a similar proportion of patients receiving VIOXX or placebo had methotrexate plasma concentrations below the measurable limit. According to the methotrexate label, methotrexate-toxicity is believed to be more dependent on time of exposure rather than peak levels. Again doctor, no dosage adjustments of once daily VIOXX and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Methotrexate (V47)

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~~is VIOXX contraindicated in patients being treated with warfarin.~~

No. Once daily VIOXX is not contraindicated in patients taking warfarin. According to the package insert, when therapy with once daily VIOXX is initiated or changed, patients should be monitored for INR\* values, particularly in the first few days. Doctor, as you know, patients on warfarin or similar agents are at an increased risk for GI bleeding when administered concomitantly with an NSAID.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If further probed, refer to the PI:

In single and multiple-dose studies in healthy individuals receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin. Standard monitoring of INR values should be conducted when therapy with VIOXX is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Submit a PIR if appropriate.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)

\*INR – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

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3- I received this letter from Searle about Celebrex and  
warfarin. What can you tell me about them VIOXX?

Doctor, for information about celecoxib and warfarin, you should talk  
to your Searle or Pfizer representative.

However, I can tell you about the concomitant use of VIOXX and  
warfarin. In single and multiple-dose studies in healthy individuals  
receiving both warfarin and rofecoxib, prothrombin time (measured as  
INR) was increased by approximately 8% to 11%. In post-marketing  
experience, bleeding events have been reported, predominantly in  
the elderly, in association with increases in prothrombin time in  
patients receiving VIOXX concurrently with warfarin. Standard  
monitoring of INR values should be conducted when therapy with  
VIOXX is initiated or changed, particularly in the first few days, in  
patients receiving warfarin or similar agents.

Finally, doctor, as you know, patients on warfarin or similar agents  
are at an increased risk for GI bleeding when administered  
concomitantly with an NSAID.

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Submit a PIR if appropriate.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI  $\Rightarrow$  Precautions  $\Rightarrow$  Drug Interactions  $\Rightarrow$  Warfarin (V51)

VIOXX PI  $\Rightarrow$  Warnings  $\Rightarrow$  GI Effects, 4<sup>th</sup> paragraph

\*INR -- International Normalized Ratios. This is a standardized way of  
measuring the degree of anti-coagulation produced by warfarin.

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~~"I'm concerned about the potential edema that occurs with VIOXX."~~

Clarify:

What are your specific concerns regarding edema?

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If the physician's concern is the overall incidence of edema with once daily VIOXX, then respond:

Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney. Clinical trials with once daily VIOXX 12.5 and 25 mg have shown renal effects such as edema similar to those observed with comparator NSAIDs. In these studies, the incidence rates for lower extremity edema were as follows: (In the AE table, point to row on edema under Body As A Whole)

VIOXX 12.5 mg or 25 mg once daily - 3.7%

Ibuprofen 2400 mg - 3.8%

Diclofenac 150 mg - 3.4%

Placebo - 1.1%

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Also, it is important to note that in these same studies the discontinuation rate due to lower extremity edema was low-0.2%.

**NOTE: Use the Renal Card to support this discussion.**

If physician is concerned about a dose related increase of edema with once daily VIOXX 50 mg, then respond:

Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney.

Regarding the safety of once daily VIOXX 50 mg, let me explain where the use of 50 mg is recommended. 50 mg is recommended for use in acute pain in adults and is not recommended for OA. In the analgesia studies, the renal effects of once daily VIOXX - such as edema-were generally similar to comparator NSAIDs.

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The 50 mg dose, while not recommended for OA, has been studied in clinical trials for up to 6 months to evaluate the GI safety of VIOXX. In these trials, the incidence of lower extremity edema was 6.3% for 50 mg. In the 6-week to 6-month studies with 12.5 or 25 mg, the incidence of lower extremity edema was 3.7% and the discontinuation rate was low-0.2%. Are you concerned about a 3.7% incidence rate of lower extremity edema in your OA patients?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Adverse Reactions ⇒ OA ⇒ Table and second paragraph (V59)

VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

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~~It is not a standard that VIOXX was denied an indication~~

Clarify: Doctor, what is your true concern?

**If physician mentions denial of an RA indication, respond:**  
Doctor, Merck was not denied any indications. Once daily VIOXX is indicated for relief of the signs and symptoms of OA, management of acute pain in adults, and for the treatment of primary dysmenorrhea. These represent all of the indications that Merck submitted to the FDA for the approval of once daily VIOXX.

(Note: If the physician ask specific question regarding the VIOXX GI Outcomes trial, you may provide the PIR with the recent bulletin, in accordance with the instructions in that bulletin, and submit additional PIRs as requested.)

*If appropriate, state:* Last month when I was in, you stated that the majority of your arthritis patients suffer from OA. I would like for us to discuss how once daily VIOXX could benefit these patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(After close: If you need information on the use of VIOXX in RA, I can submit a PIR.)

If the physician is concerned about the anti-inflammatory effect, see obstacle #6.

**Reference:**

VIOXX PI  $\Rightarrow$  Indications and Usage (V22)

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Mechanism of Action (V3)

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**6. VIOXX is not an anti-inflammatory drug.**

Doctor, the Mechanism of Action section of the package insert for once daily VIOXX clearly states: "VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models." Once daily VIOXX 12.5 and 25 mg reduced the signs and symptoms of OA as effectively as 2400 mg of ibuprofen. Also, once daily VIOXX produced significant reductions in joint stiffness upon first awakening in the morning. Doctor, as you know, morning stiffness is one indicator of inflammation.

In addition, let me point out that in the label it also states "because of the anti-inflammatory effects of VIOXX, the pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions."

Doctor, would you agree that once daily VIOXX has anti-inflammatory effects?

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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Mechanism of Action (V3)  
VIOXX PI  $\Rightarrow$  Clinical Studies  $\Rightarrow$  OA (V16)  
VIOXX PI  $\Rightarrow$  Precautions  $\Rightarrow$  General (V31)

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**Can VIOXX be used in patients using low-dose aspirin?**

There is no contraindication for concomitant use with low-dose aspirin.

Let me share with you the experience we have on the concomitant use of once daily VIOXX and low-dose aspirin. At steady state, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin.

I should also remind you that once daily VIOXX is not a substitute for aspirin for cardiovascular prophylaxis and that concomitant administration of low-dose aspirin with once daily VIOXX may result in an increased risk of GI ulceration or other complications compared with use of once daily VIOXX alone.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI  $\Rightarrow$  Precautions  $\Rightarrow$  Drug Interactions  $\Rightarrow$  Aspirin (V41)

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Understand that VIOXX has sulfonamide in its chemical structure. It is contraindicated for patients with sulfonamide allergies.

No. Doctor, let me show you the contraindications section of the label. Once daily VIOXX is not contraindicated for patients with known sulfonamide allergies, commonly known as "sulfa allergies."

Unlike once daily VIOXX, celecoxib is contraindicated in patients with sulfonamide allergies. Celecoxib contains a sulfonamide group (S-NH<sub>2</sub>), which is associated with sulfa allergies. This contraindication is based on the specific chemical structure of celecoxib and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX offers simplicity, with no sulfonamide allergy contraindication.

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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Contraindications (V23)



**Why wasn't VIOXX 50 mg studied for longer than five days in acute pain?**

To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum time for these studies for once daily VIOXX was 5 days. However, let me point out that while it is not a recommended dose for OA, once daily VIOXX 50 mg was studied out to 6 months to evaluate GI safety. In these studies, the general safety profile of once daily VIOXX 50 mg was similar to the recommended doses, except for a higher incidence of GI symptoms, lower extremity edema, and hypertension. Also, let me point out that once daily VIOXX is indicated for the treatment of acute pain. The studies that support this acute pain indication lasted up to 5 days. But as I mentioned, while it is not a recommended OA dose, once daily VIOXX 50 mg was studied for up to 6 months in OA patients – so the profile is well defined in the circular.

If further probed: **“But, I’m worried about GI safety long-term.”**  
 Doctor, in two identical studies of OA patients receiving once daily VIOXX 25 or 50 mg for up to 24 weeks, once daily VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen.

Once daily VIOXX also has GI event data from clinical trials up to one year. Among 3,357 patients who were treated with once daily VIOXX 12.5, 25, and 50 mg in controlled clinical trials of 6-weeks to 1 year, a total number of four patients experienced a serious upper GI event. Two patients experienced an upper GI bleed within 3 months (0.06%); one experienced an obstruction within 6 months; and one experienced an upper GI bleed within 12 months, for a total incidence of 0.12% over 1 year.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Clinical Studies ⇒ Analgesic Studies (V17)

VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)

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~~VIOXX cannot be used for more than five days in the management of acute pain.~~

Doctor, that is not what the circular states. The circular states that the recommended initial dose of VIOXX for the management of acute pain and the treatment of primary dysmenorrhea is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. The use of VIOXX for more than 5 days in the management of pain has not been studied.

Let me explain why these studies were designed this way. To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum duration of these studies for once daily VIOXX was 5 days.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If challenged further by the physician:

~~However, let me also point out that while 50 mg is not a~~  
recommended dose for OA, once daily VIOXX 50 mg was studied out to 6 months in OA patients. In these studies, the general safety profile of once daily VIOXX 50 mg was similar to the recommended doses for OA, except for a higher incidence of GI symptoms, lower extremity edema and hypertension.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI ⇒ Indications and Usage (V22)

VIOXX PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)

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~~16. Why did you compare VIOXX to higher doses of  
ibuprofen or naproxen rather than the management of pain?~~

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To obtain an indication for the management of acute pain in adults, a  
drug must be studied in standard pain models as defined by the FDA.  
As it states in the ibuprofen PI, in clinical studies using doses of  
ibuprofen greater than 400mg are no more effective than the 400mg  
dose in analgesia. Also, the maximum recommended dose of  
naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-  
operative dental pain and primary dysmenorrhea, once daily VIOXX  
relieved pain that was rated by patients as moderate to severe. In  
post-surgical dental pain studies, the onset of action with a single  
50mg dose of once daily VIOXX occurred within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

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Whether you're treating OA or acute pain, once daily VIOXX 12.5 mg, 25 mg, or 50 mg once daily is always a simple, one tablet, once daily dose.

Whether you're treating OA or acute pain, once daily VIOXX is always a simple, one tablet, once daily dose.

### **12.5 mg or 25 mg once daily for OA**

Once daily VIOXX 12.5mg is the starting dose for OA. If a patient requires greater pain relief, you have the flexibility to increase the dose to 25mg once daily at no additional cost to the patient.

### **50 mg once daily for Acute Pain and Primary Dysmenorrhea**

In patients with moderate to severe acute pain, the dose is 50mg once daily. Once daily VIOXX relieved moderate to severe pain following orthopedic surgery, dental surgery and primary dysmenorrhea.

In addition to the simplicity of once daily dosing, once daily VIOXX also adds the flexibility of oral suspension for both strengths.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

#### **Reference:**

VIOXX PI ⇒ Dosage and Administration (V65-V67)

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No dosage adjustment is recommended for patients with mild to moderate renal impairment. Use of once daily VIOXX in patients with advanced renal disease is not recommended because no safety information is available regarding the use of once daily VIOXX in these patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**


VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)

VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

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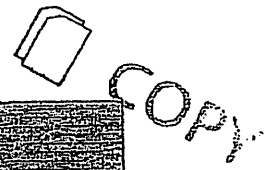
Once daily VIOXX is not offered in a single 50 mg tablet and a dosage of 50mg can be easily achieved by taking two 25 mg tablets.

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Transition back to strength, safety and QD simplicity messages.

**Reference:**

VIOXX PI ⇒ Dosage and Administration (V66)



For your reference, your time is compared to Celebrex and other  
intended NSAIDs.

Doctor, the catalog price for once daily VIOXX is \$2.02 for both 12.5  
mg and 25 mg, offering your patients one of the best values available.

The catalog price for celecoxib is \$2.38 for 100mg bid and \$2.02 for  
200 mg qd.

The catalog price for VIOXX 12.5 and 25mg is less expensive than  
the catalog prices for the usual daily doses of Arthrotec, Relafen,  
Daypro, and Voltaren.

In addition, the catalog price for the oral suspension of once daily  
VIOXX is competitive with other NSAIDs at \$3.00.

This price comparison does not establish that products have  
comparable efficacy. These prices reflect direct cost and do not  
reflect actual costs paid by consumers.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(For your reference, the average wholesale price (AWP) for once  
daily VIOXX is \$2.42 for both 12.5 mg and 25 mg. AWP for celecoxib  
is \$2.86 for 100 mg BID and \$2.42 for 200 mg qd.  
AWP for the oral suspension of once daily VIOXX is competitive with  
other NSAIDs at \$3.60.)

17 hour half-life is consistent with once daily

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The 17 hour half-life of once daily VIOXX is entirely consistent with its once daily dosing. In all OA studies, lasting from 6 to 86 weeks with 3900 patients, once daily treatment with VIOXX 12.5 and 25 mg in the morning was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg once daily, the effectiveness of once daily VIOXX was shown to be comparable to ibuprofen 800mg TID and diclofenac 50 mg TID.

If probed further on half life:

Doctor, many drugs with half-lives shorter than 24 hour are effective when dosed once a day, for example Singulair, Prinivil, and Zocor.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Excretion (V8)

VIOXX PI  $\Rightarrow$  Clinical Studies  $\Rightarrow$  OA (V16)

SINGULAIR® PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Excretion

PRINIVIL® PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Excretion

ZOCOR® PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Excretion

[REDACTED]

Copy

or

[REDACTED]

Doctor, you are correct when you say that COZAAR is metabolized by cytochrome P450 enzymes. COZAAR has been evaluated for safety in more than 3300 patients treated for hypertension. The overall incidence of adverse experiences reported with COZAAR in clinical studies was similar to placebo. No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, and phenobarbital. COZAAR has been extensively used in clinical practice and clinical study settings for over four years with millions of patients treated. Clinical experience with COZAAR is well documented.

In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

Celecoxib is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

MRK-ABR 0017674

Doctor, let me also note that VIOXX is not primarily metabolized by cytochrome P450 enzymes and is not known to inhibit enzymes of P450.

If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

COZAAR® PI ⇒ Clinical Pharmacology ⇒ General

COZAAR® PI ⇒ Adverse Reactions

COZAAR® PI ⇒ Precautions ⇒ Drug Interactions

Celecoxib PI ⇒ Precautions ⇒ Drug Interactions ⇒ General (C36)

Since Vioxx is not primarily metabolized by the  
cytochrome P450 system and there is a benefit for Vioxx  
simvastatin is not known about the fact that Vioxx is  
not primarily metabolized by the P450 system.

COP

or

How is the CYP450 system with respect to any differentiation  
ZOCOR

Doctor, you are correct when you say that ZOCOR is metabolized via  
CYP450. ZOCOR has been extensively used in clinical practice and  
clinical study settings for over 10 years with millions of patients  
treated and tens of thousands of patients studied in controlled trials.  
Clinical experience with ZOCOR is well documented.

For ZOCOR, we know that the risk of myopathy appears to be  
increased by high levels of HMG-CoA reductase inhibitory activity in  
plasma. Certain drugs that inhibit this pathway can raise the plasma  
levels of simvastatin and may increase the risk of myopathy.

Therefore, physicians contemplating concomitant therapy with  
ZOCOR and a drug that inhibits the P450 3A4 pathway should  
carefully weigh the potential benefits and risks of combined therapy  
and monitor for signs and symptoms of myopathy.

Celecoxib, on the other hand, is metabolized by P450 2C9 and is an  
inhibitor of P450 2D6. The package circular states that the co-  
administration of celecoxib with drugs that are known to inhibit 2C9  
should be done with caution. It also states that there is a potential for  
an in vivo drug interaction with drugs that are metabolized by P450  
2D6.


Doctor, let me also note that VIOXX is not primarily metabolized by  
the P450 system and is not known to inhibit the P450 system.

If you have additional questions regarding the P450 system and/or  
the implications for the products we discussed, I would be happy to  
submit a Professional Information Request to our Medical Services

Department.

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MRK-ABR 0017676

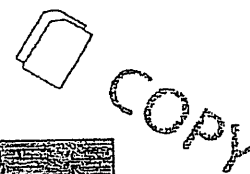
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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Metabolism (V7)  
ZOCOR<sup>®</sup> PI  $\Rightarrow$  Warnings  $\Rightarrow$  Myopathy caused by drug interactions  
Celecoxib PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Metabolism (C8)



 COPY

~~The pain studies for VIOXX were not well designed.~~

-----  
**Clarify:** Which pain study are you referring to and why do you feel it was not well designed?

- If the physician is concerned about the head-to-head study comparing VIOXX to Celebrex, offer to submit a PIR.
- If the physician is concerned because VIOXX was compared to 400 mg ibuprofen, use the response offered in obstacle #10 in the Obstacle Response Guide and respond:

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400 mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX occurred within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**


VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

- If the physician is concerned about the different dosing regimens, respond:

Doctor, this is a single dose model. It is a standard model designed to assess the analgesic effect of an agent. It was not designed to compare the dosing regimens of the agents, in this



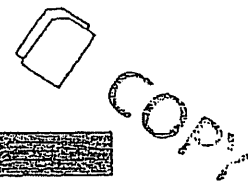
instance, once daily VIOXX versus 3 times a day Ibuprofen or twice daily naproxen. However, it does demonstrate the relative efficacy of the two agents on onset of action, peak effect, and total pain relief over 8 hours. On the measures, once daily VIOXX was generally similar to the comparator NSAIDs.

 COPY

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI  $\Rightarrow$  Clinical Studies  $\Rightarrow$  Analgesia (V17)

COPY

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**Clarify:** What specific hepatic effects are you concerned about?

**If physician is concerned about liver function testing (LFTs), respond:**

In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking once daily VIOXX 12.5 or 25 mg and 0.1% of patients taking placebo had notable elevations of ALT or AST. A patient who has an abnormal liver test while on once daily VIOXX should be monitored carefully for evidence of a more severe hepatic reaction.

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Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI  $\Rightarrow$  Precautions  $\Rightarrow$  Hepatic Effects (V32)

**If physician is concerned about metabolism, respond:**

Doctor, metabolism of once daily VIOXX is primarily mediated through reduction by cystolic enzymes in the liver. It is not primarily metabolized by the P450 system and is not known to inhibit the P450 system in the liver.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Metabolism (V7)

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MRK-ABR 0017680

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Doctor, as stated in the prescribing information, once daily VIOXX can be used concomitantly with ACE inhibitors. All NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The prescribing information for once daily VIOXX states "In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone." Remember, all NSAIDs may diminish the antihypertensive effect of ACE inhibitors. Therefore, this effect is not unique to VIOXX.

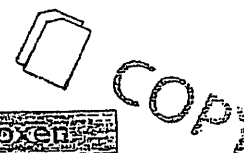
Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ ACE inhibitors (V40)

MRK-ABR 0017631

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 COPY

**VIOXX is not comparable to a single dose of naproxen.**

---

**Clarify:**

Doctor, why do you say that?

If the physician replies "It states in your product circular that VIOXX 50mg once daily was comparable to naproxen 550mg. This would seem to indicate that you are not comparable to 550mg bid," then respond:

Doctor, that statement is derived from single dose studies and is not intended to compare or draw conclusions about the efficacy of VIOXX or Anaprox over a 24 hour period. It was not designed to compare the dosing regimens of the agents. The single dose analgesia study was designed to compare time of onset, peak effect and total pain relief over 8 hours. In OA studies, once daily VIOXX 12.5mg and 25mg were comparable to ibuprofen 800mg tid and diclofenac 50mg tid. In each study, both 12.5mg and 25mg of VIOXX once daily were comparable to the comparator NSAIDs.

Would you agree that 800 mg of ibuprofen tid and 50 mg of diclofenac tid were good NSAID comparators to demonstrate the efficacy of once daily VIOXX in OA over a full 24 hours? Will you try once daily VIOXX in your acute pain and OA patients?

If the physician replies "You only compared yourself to 550mg of naproxen in your pain studies" refer to the obstacle "The pain studies for VIOXX were not well designed" in the Obstacle Response Guide, #18.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

For Representatives background, naproxen sodium is Anaprox, and naproxen is Naprosyn.

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MRK-ABR 0017682

~~2. The P450 system is the primary pathway for the metabolism of VIOXX. The P450 system is the primary pathway for the metabolism of VIOXX.~~

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I would like to clarify that in general, once daily VIOXX is metabolized primarily through reduction by cytosolic enzymes in the liver, not primarily through the P450 system. Cytochrome P450 plays a minor role in the metabolism of once daily VIOXX.

The inhibition of P450 3A4 activity by administration of ketoconazole 400 mg daily did not affect the disposition of VIOXX. However, induction of general hepatic activity by administration of the non-specific inducer rifampin 600 mg daily produced a 50% decrease in VIOXX plasma concentrations.

If you are interested in further information on the metabolism of once daily VIOXX, I'd be happy to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

---

**Reference:**

VIOXX PI  $\Rightarrow$  Clinical Pharmacology  $\Rightarrow$  Metabolism (V7)

**Background Information**


Cytochrome P450: Inhibition and Induction (referenced from the Analgesic and Anti-Inflammatory Training Program, Module 5, pages 31-32).

**Inhibition**

Inhibition of specific CYP450 enzymes can also affect the conversion of a drug to its active metabolite. Significant drug interactions may occur when NSAIDs that are metabolized through the CYP450 system are administered together with drugs that inhibit enzymes of the CYP450 systems. Concomitant administration of a drug with a known inhibitor of cytochrome P450 enzymes can alter the relative amounts of parent and metabolite that end up in the general circulation. For example, concomitant administration of fluconazole, a known inhibitor of CYP2C9, and celecoxib results in an increase in

---

celecoxib plasma concentrations due to the inhibition of celecoxib metabolism via CYP2C9 by fluconazole.

 COPY

In vitro studies indicate that celecoxib, although not a substrate, is an  
inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6. Some examples of drugs that are metabolized by CYP2D6 are certain antidepressants (e.g., tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs), antipsychotics (e.g., haloperidol), and narcotics (e.g., codeine). Coadministration of these agents with celecoxib may result in increased serum concentrations of these drugs.

### Induction

Drug-drug interactions can also occur when one drug induces the metabolism of another by increasing the synthesis or reducing the degradation of CYP450 enzymes, as shown in Figure 13. In this case, the clearance of the drug will be increased and the pharmacological effects decreased. Increased synthesis of CYP450 protein (which leads to an increase in CYP450 activity) can be associated with exposure to certain drugs or environmental agents. Enzyme induction can lead to an increased rate of drug metabolism and corresponding decreases in the availability of the parent drug. For example, indinavir is metabolized by CYP3A4. Therefore, the drug rifampin, a potent inducer of CYP3A4, should not be co-administered because it may lead to markedly diminished plasma concentrations of indinavir.

[REDACTED] about the cardiovascular effects of

**Clarify:**

What is your specific concern?

The physician may respond:

(A) "I am hesitant to use VIOXX in my patients because it may worsen CHF," or

(B) "VIOXX has the potential to increase the risk of MI."

**Response to (A) "I am hesitant to use VIOXX in my patients because it may worsen CHF."**

Doctor, as you know, there are precautions you should take when prescribing any NSAID for your patients with CHF. Because once daily VIOXX® is an NSAID, you should consider taking these same precautions when considering the use of once daily VIOXX® for this specific patient population.

Clinical trials with once daily VIOXX® 12.5 mg and 25 mg have shown renal effects such as hypertension and lower extremity edema similar to those observed with comparator NSAIDs. VIOXX® should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or edema.

(NOTE: If the physician asks about concomitant use with ACEIs, refer to Obstacle Response No. 20.)

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)

VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

**Response to (B) "VIOXX increases the risk of MI."**

MRK-ABR 0017685

Doctor, once daily VIOXX has no effect on platelet aggregation, and therefore would not be expected to demonstrate reductions in MI or other CV events. Agents such as low-dose aspirin are routinely prescribed for CV patients for their effect on the inhibition of platelet aggregation. Therefore, once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis. However, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

(Refer to Obstacle Response No. 7.)

If probed further:  
Offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

~~VIOXX PI ⇒ Precautions ⇒ Aspirin (V41)~~

MRK-ABR 0017686



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24. How did it state that VIOXX provided a significant reduction in  
pain after 1 to 2 weeks? Why should I use VIOXX when  
I have a condition that has achieved significant reduction of  
pain after 1 to 2 weeks with other dosing?

Doctor, it is important to note that the time period you refer to, 1 to 2 weeks, was the predetermined initial time intervals in the study at which pain relief was measured. Patient's pain relief was simply not assessed earlier than that by design. The objective of these trials (up to one year) was to evaluate study endpoints over the course of the trial-not onset of action. These were not studies of onset of action

If you would like specific information on the onset of action of once daily VIOXX in acute pain, let's look at the comparison to naproxen sodium (Anaprox) in dental pain which showed an onset of action of VIOXX 50 mg within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Reference:**

VIOXX PI=Clinical Studies PI=OA (V16)

VIOXX PI=Clinical Pharmacology = Pharmacokinetics = Absorption (V4)

VIOXX PI=Clinical Studies=Analgesia, including Dysmenorrhea (V17)

Celecoxib PI=Clinical Pharmacology = Pharmacokinetics = Absorption (C4)

 COPY

~~Do not use VIOXX® pre or post-operatively?~~

**Clarify:** Dr. what specifically is your concern?

**If the concern is with bleeding time (pre and post-operatively), respond:**

Once daily VIOXX® has not been studied in a pre-operative setting. I cannot make a recommendation regarding pre-operative use.

In studies of healthy volunteers who had not undergone surgery, at multiple doses of up to 375 mg daily up to 12 days, VIOXX® had no effect on bleed time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000mg of VIOXX®.

Additionally, VIOXX® 50 mg has shown no effect on platelet aggregation. Also, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

**If requesting further information, please submit a request.**

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**If the concern is the management of acute pain, post-operatively, respond:**

In order to obtain an acute pain indication, VIOXX® was demonstrated to provide effective pain relief in 3 acute pain models.

Two of the pain models involved surgery – the post-orthopedic surgical model and the post-operative dental pain model. The post-orthopedic surgery studies involved patients with knee or hip replacement. Patients received their first dose of VIOXX®, on average, 46 hours after surgical procedure (range 17 to 97 hours). In our acute dental pain study, VIOXX® provided onset of pain relief within 45 minutes.

Dr., in contrast, Celebrex is not indicated for the management of acute pain.

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If further information is requested, offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

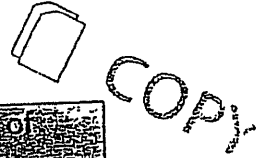
**Reference:**

*VIOXX PI ⇒ Clinical Studies ⇒ Platelets (V21)*

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~~260 Use VIOXX. I'm concerned about the safety profile of~~

Clarify:

Doctor, specifically what safety concerns are you referring to?

If the physicians' concern is renal safety or edema:  
Refer to obstacle # 12, 4

If the physicians' concern relates to hepatic effects or  
cardiovascular safety:  
Refer to obstacle # 19,23

If the physicians' concern is whether the rate of ulcers increases over  
time when treating patients with VIOXX, respond with the following:

Doctor, in order to address your concerns, I would like to discuss the  
extensive GI endoscopy program that has been conducted for  
VIOXX®. In two identical, large trials, the **cumulative** incidence of  
ulcers with patients taking VIOXX 25 mg and 50 mg once daily (2 to  
4X the dose used for osteoarthritis) was studied. The results with  
VIOXX showed significantly fewer endoscopic ulcers than with  
ibuprofen 2400 mg at weeks 12 and 24. (Refer to VIOXX® PI, Clinical  
Trials.)

Doctor, I would like to bring to your attention a few important factors  
regarding our endoscopy study design:

First, "cumulative rates" include all patients who develop an ulcer up  
to a specified point in time. In other words, the rates shown at week  
24 include all endoscopic ulcers detected by week 12 and all  
endoscopic ulcers detected between weeks 12 and 24. This method  
assures that patients developing ulcers at any time during the study  
are represented in the overall risk assessment.

As noted in the attached Laine reprint (page 780, second full  
paragraph), when referencing the endoscopy trials for VIOXX®,

*"Ulcer rates in the first 3 months of the study were not significantly different compared to the second three months in the rofecoxib groups or in the ibuprofen groups (4.1% vs. 5.5% in the 25 mg rofecoxib group, 7.3% vs. 7.4% in the rofecoxib 50 mg group, and 27.7% vs. 18.2% in the ibuprofen group)". Please refer to the Important Considerations for Endoscopy Studies as noted in the detail aid.*

**Please provide appropriate and referenced balancing throughout product discussions with healthcare professionals.**

**Note:** We have heard reports from the field that Searle/Pfizer representatives are describing the results as "additive rates". Additive rates evaluate an increase over a specified period of time and make assumptions that rates continue to increase by the same rate into the future.

The rates reported in this study are not additive rates.

MRK-ABR 0017691

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Why are you telling me not to prescribe Celebrex for sulfa  
allergic patients when Hyzaar has the same  
contraindication?

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Dr., I can appreciate your concern. Let me clarify Merck's view of this and every other contraindication for our product.

The fact remains that a contraindication is just that – a contraindication. At no time will Merck ever suggest that you prescribe an agent to a patient who is contraindicated for its use.

As you know, use of hydrochlorothiazide in patients who are allergic to sulfonamides is contraindicated. Hyzaar, which is losartan plus hydrochlorothiazide, is contraindicated for use in patients with hypersensitivity to other sulfonamide-derived drugs. However, losartan, (Cozaar) alone is not contraindicated in these patients. We do not, have not, and never will recommend the use of Hyzaar for patients who have sulfonamide allergies. Cozaar is not contraindicated for patients who have a sulfonamide allergy and can be prescribed for these patients who need control of their BP.

Regarding the Coxib class, **VIOXX does not have a contraindication for sulfonamide allergic patients – Celebrex does.**

(Note: If you have not already discussed Cozaar/Hyzaar with this physician on this call, take the opportunity to initiate a discussion regarding these products after you close your product discussion for VIOXX. One suggested transition may be, "Just as we have discussed appropriate patients to prescribe VIOXX for, I'd like to discuss appropriate patients for therapy with Cozaar, Hyzaar 50/12.5 and Hyzaar 100/25...")

MRK-ABR 0017692

27. The two recent JAMA articles showed Celebrex provided greater reductions in events than VIOXX. Or it looks like there are still a lot of PUBs in the VIOXX group. Why is the effect on VIOXX not significant?

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**Note:** Physician is referring to the JAMA article, November 24, 1999 issue, Volume 282, No. 20

**Representative Response:**

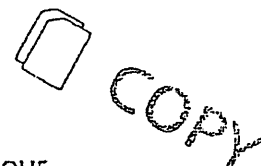
Actually those were different types of studies. (See below or in the cover bulletin for background information)

The JAMA article on VIOXX is a combined analysis of PUBs, Perforation, symptomatic Ulcers and Bleeds from all 8 double bind, randomized phase 2b/3 OA trials. The Celebrex article, which is the information currently contained in their PI, is a prospective endoscopy trial with Celebrex, comparator NSAIDs and placebo. This is similar to the study I have been discussing with you from our package circular, which compares VIOXX to Ibuprofen, and placebo. The JAMA study on VIOXX was designed to compare VIOXX to the comparator NSAIDS, not placebo. No one knows what the background rate of PUBs in patients treated with placebo would be, but we know it is not zero. It would be inaccurate to compare the JAMA articles on VIOXX and Celebrex because the endpoints (ulcers detected on surveillance endoscopy versus clinically significant events) are entirely different. Until head to head comparative trials are designed and completed, no conclusions can be drawn regarding relative GI safety between these agents.

Additional studies will need to be conducted to further support these conclusions. As stated in the VIOXX package insert (under the 044 endoscopy data), "the correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established."

MRK-ABR 0017693





However, I can share with you information for VIOXX from our endoscopy trials. These results are listed in our package circular, in our detail aids and most recently were published in Gastroenterology. The lead author of the study was Dr. Loren Laine. Among 742 OA patients without ulcers on baseline endoscopy, the cumulative incidence of gastroduodenal ulcers  $\geq$  3mm with VIOXX (25 mg or 50 mg) was significantly ( $p < 0.001$ ) lower than ibuprofen.

Also, in controlled clinical trials summarized in our promotional literature, among 3357 patients who were treated with VIOXX 12.5 mg, 25 mg, and 50 mg, only (POB data):

- 2 of 3357 (0.06%) patients experienced a serious Clinical Upper GI event in the first 3 months
- and 4 of 3357 patients cumulative (0.12%) experienced a serious Clinical Upper GI event in the first 12 months.

---

Transition back to Laine reprint or detail aid to further discuss results with VIOXX and deliver Top 5 messages, provide appropriate balance and close the call.

Remember that you may not discuss or provide the JAMA article to your physicians. You must submit a PIR to address any additional concerns.

#### Background Information:

It is critical to understand the differences in the types of analyses that have been performed in the studies that are now being published in JAMA and Gastroenterology. Merck and Searle have both performed endoscopy studies comparing VIOXX® and celecoxib to NSAIDs. Both companies also have data from their combined clinical trials in their PIs describing what are termed "serious" upper GI events (Perforations, Obstructions and Bleeds, or POBs). These events are found during the course of clinical treatment, NOT during a scheduled endoscopy. In addition, Merck has just





published in JAMA the results of a PUB (Perforations, symptomatic Ulcers and Bleeds) analysis, data which is not in the PI for VIOXX®.

The first type of analysis is the endoscopy study. In this study patients are randomized to study drugs (or placebo) and undergo scheduled endoscopies (in the VIOXX® trials these were at baseline 6, 12, and 24 weeks). Ulcers that are seen through the endoscope are measured and counted. This provides a basis for comparing the effect of drugs on the gastric mucosa and is seen as a surrogate for clinically significant events, even if the ulcers seen are not symptomatic and do not actually lead to bleeding or other complications. This is the type of analysis done in the Laine paper published in Gastroenterology and the Searle paper in JAMA, data in the PIs for both VIOXX® and celecoxib.

It is sometimes considered more clinically relevant to compare drugs based on the number of clinical events that occur. Thus the second type of analysis is done, looking at events that occur during the trials. These occur at much lower rates than endoscopically visualized ulcers, so it requires many more patients to see any differences between drugs. Merck chose to measure PUBs (perforations, ulcers and bleeds) while the clinical event data in the PIs for VIOXX® and celecoxib measured POBs (perforations, obstructions and bleeds). The primary difference between these is the U – Ulcers that present due to clinical signs or symptoms. In the Merck JAMA paper, if any patient underwent endoscopy for cause (that is, the patient demonstrated symptoms that the physician judged worthy of follow-up) and ulcers were detected, these were included as events, along with the POBs. This explains why the rates of POBs in the PIs for celecoxib and VIOXX® are lower than the PUB rates shown in the JAMA paper on VIOXX®.

MERCK-ABR-0017695

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Doctor, it would have been great news for patients if Celebrex received an indication to prevent cancer, but what Celebrex actually received was an indication for a rare genetic disorder, familial adenomatous polyposis (FAP).

The indication is:

"to reduce the number of adenomatous polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care". The indication further states, "It is not know whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients." The label also states that "treatment with Celebrex in FAP has not been shown to reduce the risk gastrointestinal cancer or the need for prophylactic colectomy or other FAP -related surgeries."

If pressed about whether Merck is conducting studies state,

"Doctor, I am not permitted to discuss uses that not included in the labeling for VIOXX. If you would like, I can submit a request for information to our medical services department."

Transition back to the HI COXIB or HI NSAID messages for VIOXX using the following statement, "So you can see, doctor, this is a new indication for a very rare disorder. Let's discuss much more common disorder-OA."

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MRIC-ABR 0017696

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Dr. Searle/Pfizer has presented me with new data which showed that Celebrex 400mg bid, the dose used in the FAP studies, had an adverse event profile "similar to that reported for patients in arthritis controlled trials". It is important to realize that the FAP study included 83 patients, who were generally younger and otherwise healthy. This is a population very different from the patient population of OA studies.

Note: You may have to probe to uncover the real obstacle. It may be presented as one of the following:

- Celebrex is now proven to be safer than VIOXX.
- Celebrex is a safer agent.
- Are there safety issues with VIOXX?

#### CLARIFY FIRST:

"Doctor, what is your concern regarding VIOXX? Is there a particular area of concern you want to discuss?"

#### RESOLVE

Doctor, Searle/Pfizer may be using their new FAP data to suggest that Celebrex 400mg bid, the dose used in the FAP studies, had an adverse event profile "similar to that reported for patients in arthritis controlled trials". It is important to realize that the FAP study included 83 patients, who were generally younger and otherwise healthy. This is a population very different from the patient population of OA studies.

It is important to realize that VIOXX 50mg is the recommended dose for acute pain or analgesia, and not a recommended dose for OA. In fact, our product circular states,

*"Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the*

*analgesia studies was generally similar to those reported in the  
osteoarthritis studies."*

*COPY*

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Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in osteoarthritis studies.

**If the doctor refers to the increased incidence of edema or hypertension listed under the Adverse Experiences table:**

Doctor, the data that you are referring to are from the use of VIOXX 50mg in two, 6-month, OA, endoscopy trials, which evaluated the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to determine GI safety. VIOXX, at both 25 and 50mg doses, yielded significantly fewer endoscopic ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension and edema was similar to that reported in the OA studies with VIOXX 12.5 and 25mg.

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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

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MRK-ABR 0017698

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PROTECTIVE ORDER IN  
ABRUSLEY V. MERCK, et al.  
(02-0195 W.D. La.)

 COPY

[REDACTED]

**Clarify:**

Doctor, what has led to your concern that VIOXX causes dose-related increases in hypertension?

**Resolve:**

Doctor, according to the product circular for VIOXX, the incidence of hypertension reported in OA studies, regardless of causality, was 3.5% with the 12.5 or 25mg dose. For patients who were treated with VIOXX 50mg in analgesia studies, the VIOXX product circular states,

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*"Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies."*

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in OA studies. VIOXX 50mg is not a recommended dose for OA.

**If the doctor refers to the increased incidence of hypertension listed under the Adverse Experiences table:**

Doctor, the data that you are referring to is from the 6-month, OA, endoscopy trials, which were used to evaluate the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to evaluate GI safety. VIOXX, at both 25 and 50mg doses yielded significantly fewer endoscopic

ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension was similar to that reported in the OA studies with VIOXX 12.5 and 25mg.



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Doctor, have I addressed your concern with dose-related increases in hypertension with VIOXX?

Now let's talk about the benefits VIOXX offers you and your patients in the treatment of OA and acute pain.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

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MRK-ABR 0017700

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ABRUSLEY V. MERCK, et al.  
(02-0196 W.D. La.)



32) VIOXX must be a safer agent. Unlike VIOXX, Celebrex  
 clinical trial data did not show any increases in myocardial  
 infarction or stroke.

COPY

The design of the studies differed in a number of significant respects and therefore the results of the two studies cannot be compared. So, let me tell you about the data for VIOXX from our OA clinical trials at the 12.5 mg and 25 mg doses.

In an extensive review of all of our Phase III OA clinical trials, VIOXX did not show an increase in the incidence of thromboembolic events compared to placebo or the comparator NSAIDS.

You can feel confident that Merck has conducted OA clinical trials for VIOXX 12.5mg and 25mg daily in over 3600 patients with OA; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. These trials included a placebo arm in the six week studies and two comparator NSAIDS, ibuprofen 2400 mg and diclofenac 150 mg daily. VIOXX 12.5mg and 25mg has shown to provide OA pain relief all day, all night and into the next morning.

Referring to the Adverse Events data, as listed in the package insert for VIOXX 12.5 mg and 25mg daily, the only Cardiovascular System adverse event experienced as occurring over 2% (in trials of six-weeks to six-months) was hypertension at 3.7 % vs. comparators of ibuprofen 2400 mg daily at 3.0% and diclofenac 150 mg daily at 1.6%. In addition, stroke and MI each occurred in less than 0.1% of patients taking VIOXX in our OA clinical program.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

**Note:** If the physician has questions regarding the hypertension & edema rates for VIOXX, please refer to obstacles #19 & #12. Also, the Renal Card (OAN #001962(1)) is an excellent resource that has been developed to directly address issues pertaining to hypertension & edema.

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~~Merck announced only preliminary results of the VIOXX OUTCOMES study. Data analysis is on-going. The final results with corresponding p-values and incidence rates will be presented later this year.~~

MRK-ABR 0017702

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By more and that the new COX-2 drug, Mobic, was not  
and is not

Doctor, Mobic is a non-steroidal anti-inflammatory drug – an NSAID – that inhibits both COX-1 and COX-2 at its therapeutic doses. It does not selectively inhibit COX-2.

If the doctor continues and asks how Mobic differs from VIOXX, respond:


Doctor, VIOXX is indicated for the signs and symptoms of OA, acute pain in adults, and primary dysmenorrhea. Mobic is indicated for OA. VIOXX is available in three tablet strengths, 12.5 mg, 25 mg, and 50 mg, which allows you to prescribe VIOXX one tablet, once daily for all indications. Mobic is available in a 7.5 mg tablet; to increase the dose requires two 7.5 mg tablets. Finally, the two OA doses of VIOXX – 12.5 mg and 25 mg – are priced the same. The highest dose of Mobic is twice as expensive as the lowest dose because patients must take two tablets.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Alternatively, if the doctor continues and asks how Mobic's mechanism of action that you just explained differs from that of VIOXX, respond:

Doctor, VIOXX is an NSAID that inhibits COX-2 without inhibiting COX-1 at therapeutic doses. Of course, Doctor, we would not recommend that you base your prescribing decision on the mechanism of action of the drug. Can I take a minute and share with you the clinical data on the Strength, Safety, and QD Simplicity of VIOXX?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

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1. The COXIB of choice is VIOXX because MOBIC is 20% less  
SUBJECT TO THE PROTECTIVE ORDER IN ABRUSLEY V. MERCK, et al.  
THE COXIB OF CHOICE IS VIOXX BECAUSE MOBIC IS 20% LESS

Doctor, if cost is your reason for considering Mobic, let me point out that Mobic is available only in a 7.5mg tablet. That means that if you need to increase your patients dose to 15mg, the maximum recommended dose for OA, your patients cost will double. In contrast, VIOXX 12.5 and 25 mg tablets are flat priced so you can select the appropriate dose for your OA patients without regard to cost.

Let me share with you the benefits that VIOXX can provide for you and your patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

MRK-ABR 0017704

Not impressed with VIOXX's tremendous amount of  
worldwide experience.

COPY

Doctor, I can understand that experience with a medication is very important to you. The most valuable experience is not just what has happened abroad, but the clinical experience that you and your colleagues have developed on your own. What has been your experience with VIOXX over the last year? Have you been satisfied with your clinical experience using VIOXX over the last year?

In the last year, VIOXX has achieved a vast amount of clinical experience among many specialties-Rheumatologists, Orthopedic Surgeons, Gastroenterologists, Internists, and Primary Care Physicians. VIOXX has become second most prescribed branded NSAID in the U.S. in less than one year. Is this the kind of experience that is important to you?

Not only has VIOXX developed a tremendous amount of clinical experience within the U.S., but VIOXX has been extensively studied in clinical trials. Let me share some data with you demonstrating the safety and efficacy of VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX. Be sure to emphasize the data within your Core Visual Aid as you deliver these messages. Focus on the number of patients within each study and the benefit which the results present for the doctor's patient.

Remember to provide appropriate balancing information as part of all product discussions.

MIRK-ABR 0017705

17 The MOBIC representative has shown data from two large  
20 studies, the MEUS and SELECT trials, which  
21 showed that MOBIC's tolerability in these studies was  
22 comparable to ibuprofen.

Doctor, I can understand that when choosing a medication to treat  
your OA patients, you would want to choose a medication with a well  
documented GI safety and tolerability profile.

Doctor, the studies which you're referring to are not reflected in the  
prescribing information for MOBIC. I believe that those studies only  
lasted 28 days, did not include endoscopic data, and only included  
the 7.5mg dose of MOBIC.

Let me remind you of the extensive GI data available for VIOXX. In  
two studies involving over 1500 patients, VIOXX demonstrated  
significantly fewer endoscopic ulcers than ibuprofen and was  
consistent across all studies. These studies lasted 6 months, and the  
incidence rate of ulcers in groups receiving VIOXX did not increase  
over time. These studies were done with the 25mg and 50mg dose of  
VIOXX, although I want to remind you that the 25mg dose is the  
maximum recommended dose for chronic OA.

Does the duration and inclusion of endoscopy data in the VIOXX  
studies cause you to be more impressed with the data for VIOXX than  
that of MOBIC?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part  
of all product discussions.

MRK-ABR 0017706



[REDACTED]

Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.4% with VIOXX and 0.1% with naproxen. Upon further analysis, four percent of patients in the VIOXX GI Outcomes Study had experienced a cardiac event such as a heart attack or stroke before entering the study and thus met the established criteria for the use of aspirin for secondary CV prophylaxis. In the remaining 96% of patients for whom aspirin was not indicated for secondary CV prophylaxis, the incidence of MI was lower—0.2% for VIOXX and 0.1% for naproxen. This difference was not statistically significant.

In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. They also presented data for patients who were not prescribed aspirin. In this group, the incidence of MI was 0.2% for Celebrex and 0.1% for the comparator NSAIDs. Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations.

MRK-ABR 0017707

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

 COPY

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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

NOTE: There will be an additional PIR to address these issues available shortly.

**If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them,**

In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.